REMARKS

I. Introduction

In response to Applicants' last response, dated November 15, 2004, the PTO has maintained certain rejections as discussed below. Applicants respectfully request reconsideration of the present application in view of the following reasons.

II. Status of the Claims

No claims are amended. Claims 1-22 and 25-54 are pending.

III. The Office Action

The PTO maintained three rejections of various groupings of the claims. These are discussed below in the order presented in the Office Action.

A. Rejection of Claims Under 35 U.S.C. § 102(b)

1. Desieno

Claims 1, 2, 8-10, 13, 14, 30, 31, and 34-53 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by U.S. Pat. No. 5,573,783 to Desieno *et al.* ("Desieno"). In maintaining this rejection, the PTO alleged that Desieno inherently teaches the claimed rate controlling polymer. This is so, argues the PTO, because although Desieno does not expressly teach such a polymer, the reference nonetheless evidences the claimed controlled release aspect of the polymer by virtue of the disclosed overcoated compositions exhibiting "decreased gastrointestinal irritancy" and "physical protection for the drug layer". Office Action at page 7 (quoting Desieno at col. 8, lines 43-46, and col. 18, lines 4-8). Applicants respectfully traverse the rejection.

Desieno does not anticipate the claims because the reference neither expressly teaches the claimed rate controlling polymer, nor does it inherently do so.

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such [a] gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991). The PTO and Applicants agree here that Desieno is "silent" about the claimed rate-controlling polymer and resultant controlled release nanoparticulate composition. Additionally, the PTO has not made recourse to any evidence other than Desieno itself to support the allegation of the presence of the rate-controlling polymer.

Ironically, the PTO specifically relied upon passages within Desieno that not only do not support the rejection, but they also undermine the necessity element that is central to applying the doctrine of anticipation by inherency. Specifically, Desieno discloses a "PVP/PEG overcoat that provides physical protection for the drug layer coated on the bead." Desieno at col. 18, lines 5-7. By contrast to the PTO's assertion, this passage suggests absolutely nothing about the overcoat conferring controlled release properties to the disclosed compositions. This must be so because the PTO's redaction of Desieno omitted an explanation that the overcoat does not "inhibit[] redispersion of the drug in aqueous media." *Id.* at co. 18, lines 7-8.[1] What worse support could exist for the proposition of the overcoat polymer conferring a controlled release property than the reference itself stating precisely the contrary?

The second passage upon which the PTO relied also discredits the notion of there being an inherently disclosed rate-controlling polymer. In this regard, Desieno "contemplated that the drug particles of this invention provide *more rapid onset of drug action* and decreased gastrointestinal irritancy." Desieno at col. 8, lines 43-46 (emphasis supplied). The PTO's characterization of Desieno omitted the italicized and crucial portion of the quote above: the compositions are intended to result in the rapid availability of the nanoparticulate drug. *See also* Desieno at col. 8, lines 40-41 ("the pharmaceutical compositions . . . exhibit unexpectedly high bioavailability . . .").

Moreover, Desieno further suggests that the disclosed compositions *rapidly release* the nanoparticulate active agents, e.g., in about 10 minutes, which is much quicker than the claimed range of about 2 to about 24 hours. *See* Desieno at col. 17, line 55, to col. 18, line 3 (procedure to determine ease of resconstituting particles).

In summary, Desieno does not inherently disclose the claimed rate controlling polymer. This is because Desieno describes the polymeric overcoating as a protective feature that does not impede

[1] Desieno further suggests that the disclosed compositions *rapidly release* the nanoparticulate active agents, e.g., in about 10 minutes, which is much quicker than the claimed range of about 2 to about 24 hours. *See* Desieno at col. 17, line 55 to col. 18, line 3 (procedure to determine ease of resconstituting particles).

the rapid dispersing of the nanoparticulate drug composition. Consequently, a rate controlling polymer is not "necessarily present" in the compositions disclosed by Desieno. The reference thus fails to support the rejection, and Applicants therefore respectfully request the PTO to reconsider and withdraw the same.

2. Vernon

Claims 1, 2, 8, 9, 13, 14, 30, 31, 34-38, 41, 42, 45, 46, 49, 50, and 53 stand rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by WO 95/22318 to Vernon ("Vernon"). In maintaining this rejection, the PTO pointed out the reference's teaching a particle size of 100 nm to 100,000 nm (*i.e.*, 100 μm) that falls within the claimed range of less than about 1000 nm. The PTO additionally drew Applicants' attention to a polymeric overcoating that Vernon discloses as conferring controlled release properties to the coated composition. Applicants respectfully traverse the rejection.

Vernon does not anticipate the claims because the reference fails to teach the claimed "at least one surface stabilizer associated with the surface of the nanoparticulate drug . . ." (claim 1). Vernon discloses a drug that is suspended in a polymer matrix of at least two water soluble and biodegradable polymers. *See* Vernon at page 2, lines 4-12. However, in contrast to the claimed invention, Vernon does not teach or suggest that the drug is poorly soluble, that it is in nanoparticulate form, and that at least one surface stabilizer is associated with the surface of the drug nanoparticle. Thus, Vernon does not disclose every feature of the claimed invention and, therefore, the reference does not anticipate the claimed invention. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw the rejection.

B. Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1-22 and 25-53 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Desieno in view of U.S. Pat. No. 5,145,684 to Liversidge *et al.* ("Liversidge) and U.S. Pat. No. 5,811,388 to Friend *et al.* ("Friend"). In maintaining this rejection, the PTO was helpful in clarifying that Desieno is the primary reference. The PTO further clarified that Liversidge is cited solely to acknowledge the definition of the particle size distribution recited in, e.g., claim 1, while Friend is cited solely to address the concentration and identity of rate controlling polymer specified in certain dependent claims. Applicants respectfully traverse the rejection.

For all of the reasons discussed above in the context of the section 102(b) rejection, Desieno does not teach or suggest the claimed controlled release nanoparticulate compositions. Moreover, Desieno teaches *away* from Applicants' claimed invention because Desieno and Liversidge evidence the conventional wisdom in the art that nanoparticulate drug compositions are desired precisely because of their rapid release characteristics. Thus, a person of ordinary skill in the art would know that nanoparticulate drug compositions provide immediate and fast release of the drug as a consequence of the nanoparticle drug size. *See, e.g.,* Liversidge at col. 1, lines 28-35. Stated practically, nanoparticulate compositions give rise to "unexpectedly high bioavailability" and "rapid onset of drug action." Desieno at col. 8, lines 42-44. The motivation to prepare nanoparticulate drug compositions is especially strong for poorly soluble drugs, as presently claimed, because this subclass of drugs typically exhibits poor bioavailability and slow dissolution times. *See* Liversidge at col. 1, lines 13-27.

A person of ordinary skill in the art therefore would not have been motivated to make a *controlled release* nanoparticulate composition of a poorly soluble drug. Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *See In re Hedges*, 783 F.2d 1038, 1041, 228 USPQ 685, 687 (Fed. Cir. 1986). *Cf. United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 484 ("known disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account when determining obviousness"); *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 958, 43 USPQ.2d 1294, 1297 (Fed. Cir. 1997) ("conventional wisdom that a combination should not be made is evidence of unobviousness.").

In this context, the person of ordinary skill would not have been motivated to formulate a known *rapid release* nanoparticulate composition into a *controlled release* form because the whole point of making nanoparticulate compositions of poorly soluble drugs is to overcome their inherently slow release properties. As discussed in Applicants' previous response, Friend does not address any nanoparticulate compositions, and therefore has no suggestive value in this regard. Consequently, the person of ordinary skill would not have considered Applicants' invention to have been obvious.

For all of these reasons, Desieno, alone or in combination with either Liversidge or Friend, does not render obvious Applicants' claimed invention. Accordingly, Applicants respectfully request the PTO to reconsider and withdraw this rejection.

IV. Conclusion

Having addressed each outstanding issue, Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. Applicants invite the Examiner to contact their representative undersigned below by telephone if the Examiner feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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By 

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.